APPENDIX D

REVIEW

Approaches to the Preparation of Enantiomerically Pure (2*R*,2'*R*)-(+)-*threo*-Methylphenidate Hydrochloride

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Abstract: Various approaches to the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) are reviewed. These approaches include synthesis using enantiomerically pure precursors obtained by resolution, classical and enzyme-based resolution approaches, enantioselective synthesis approaches, and approaches based on enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate followed by epimerization at the 2-position.

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Keywords: attention deficit hyperactivity disorder; enantioselective synthesis; enzymatic hydrolysis; (2*R*,2'*R*)-*threo*-methylphenidate; resolution; ritalin

1 Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed behavioral disorder in children. ADHD persists across the full span of development, from preschool to school age and adolescence, and frequently continues into adult life.[1] The diagnosis of ADHD is a clinical rather than a specific medical diagnosis. To date there are no laboratory tests that can be used to make a definitive diagnosis of ADHD.[2,3] Racemic (±)-*threo*-methylphenidate hydrochloride [Ritalin® hydrochloride, methyl phenyl-(2-piperidyl)acetate] is a mild nervous system stimulant and is currently the most widely used drug for the treatment of children with ADHD.[4,5] The psychostimulant properties of (±)-*threo*-methylphenidate have been linked to its binding to a site on the dopamine receptor, resulting in inhibition of dopamine re-uptake and enhanced levels of synaptic dopamine. This stimulation is believed to regulate attention and impulsivity of ADHD in children. Racemic (±)-*threo*-methylphenidate, however, possesses side effects, e.g., anorexia, insomnia, weight loss, dizziness, dysphoria, and has potential for substance abuse in patients, especially when administered intravenously or through inhalation as it produces an euphoric effect. It has been postulated that the euphoric effect of (±)-*threo*-methylphenidate is primarily due to the action of L- or (2*S*,2'*S*)-(−)-*threo*-enantiomer. Enhanced relief for patients with ADHD was recently documented[6] with newly formulated D- or (2*R*,2'*R*)-(+)-*threo*-methylphenidate (Figure 1), while reducing side effects and euphoric effects. Additionally, it has been shown that (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) is more potent in the induction of locomotor activity and has a higher affinity for the dopamine transporter than the (2*S*,2'*S*)-(−)-*threo*-enantiomer 2.[7] A recent report has demonstrated that pharmacological specificity resides entirely in the (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) and that the binding of the (2*S*,2'*S*)-(−)-*threo*-enantiomer 2 in human brain is mostly non-specific.[8] This was further confirmed by positron-emission tomography (PET) images of human brain after administration of [^{11}C]-(2*R*,2'*R*)-(+)-*threo*-methylphenidate and [^{11}C]-(2*S*,2'*S*)-(−)-*threo*-methylphenidate, which showed that the [^{11}C]-(2*R*,2'*R*)-(+)-*threo*-enantiomer concentrated in basal ganglia, where it binds to the dopamine transporter.

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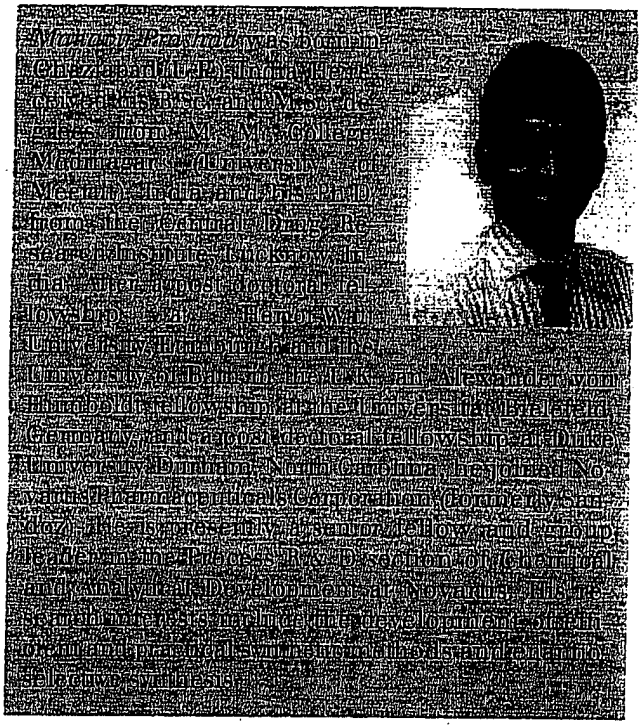


The [^{11}C]-(2*S*,2'*S*)-(−)-*threo*-enantiomer did not bind, indicating that the (2*R*,2'*R*)-(+)-*threo*-enantiomer **1** is the active form.[9] Thus, to segregate the desired pharmacological activities from side effects, there is a great interest for preparing enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) on a large scale.

From the historical perspective, racemic methylphenidate was first synthesized (Scheme 1) in 1944 by Panizzon[10,11] and was originally marketed as a mixture of two racemates: 80% of (±)-*erythro* and 20% of (±)-*threo*. Subsequent studies led to the discovery that the central stimulant activity was associated with only one, i.e., the (±)-*threo* racemate[11–13] and that the (2*R*,2'*R*)-(+)-*threo*-enantiomer was 5[13] to 38[14] times more active than the (2*S*,2'*S*)-(−)-*threo*-enantiomer. The metabolic pathway for methylphenidate in dogs and rats has also been delineated.[15] While the development of efficient routes for the synthesis of racemic (±)-*threo*-methylphenidate and its analogues for structure-activity relationship studies remains a topic of interest,[16–19] this review focuses only on the approaches reported to date for the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**).

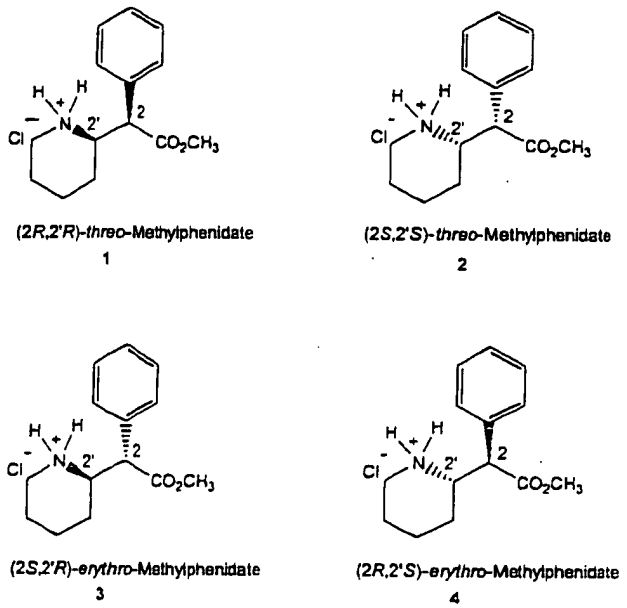


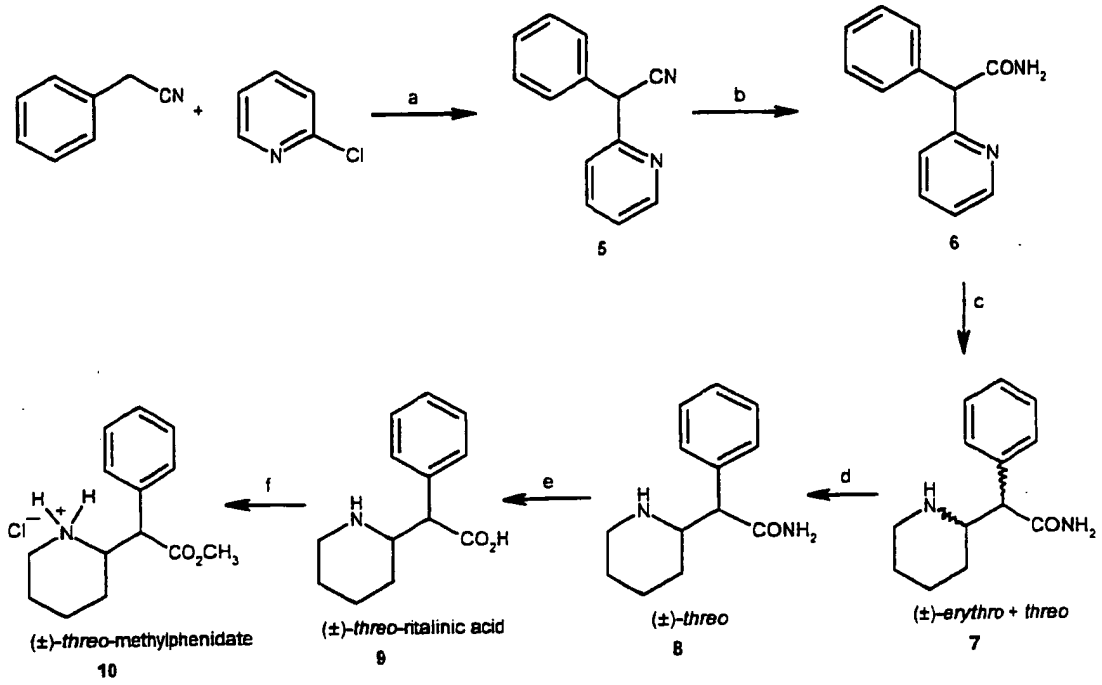
Figure 1.

2 Methods for the Enhancement of Enantiomeric Purity of Enriched 1

Enrichment of the enantiomeric purity of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) was first reported by Patrick et al. by crystallization from a mixture of methanol and ether.[7] We (Novartis) also recently reported that the enantiomeric purity of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride salt (**1**) was enhanced from 80% ee to >98% ee by recrystallization from a mixture of methanol and *t*-butyl methyl ether (1:1.7 v/v).[20] An enrichment of the enantiomeric purity of **1** from this solvent mixture was then reported by Faulconbridge et al.[21] Thus, any approach which yields enriched (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) would afford enantiomerically pure **1** after recrystallization from this solvent mixture, but at the cost of loss in yield.

3 Approaches Using Enantiomerically Pure Precursors Obtained by Resolution

The first preparation (Scheme 2) of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) was reported by R. Rometsch of former Ciba Pharmaceuticals (now Novartis).[12,15] Enantiomerically pure L-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (**12**), obtained by the resolution of (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (**11**) with D-(−)-tartaric acid in 96% ethanol, was subjected to epimerization to the desired (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (**13**) with aqueous KOH. (2*R*,2'*R*)-*threo*-2-Phenyl-2-(2-piperidyl)acetamide (**13**), thus obtained, was converted to the desired (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) by hydrolysis and esterification. This approach has recently been further optimized by Ramaswamy and Kheta-



(±)-*erythro* + *threo*

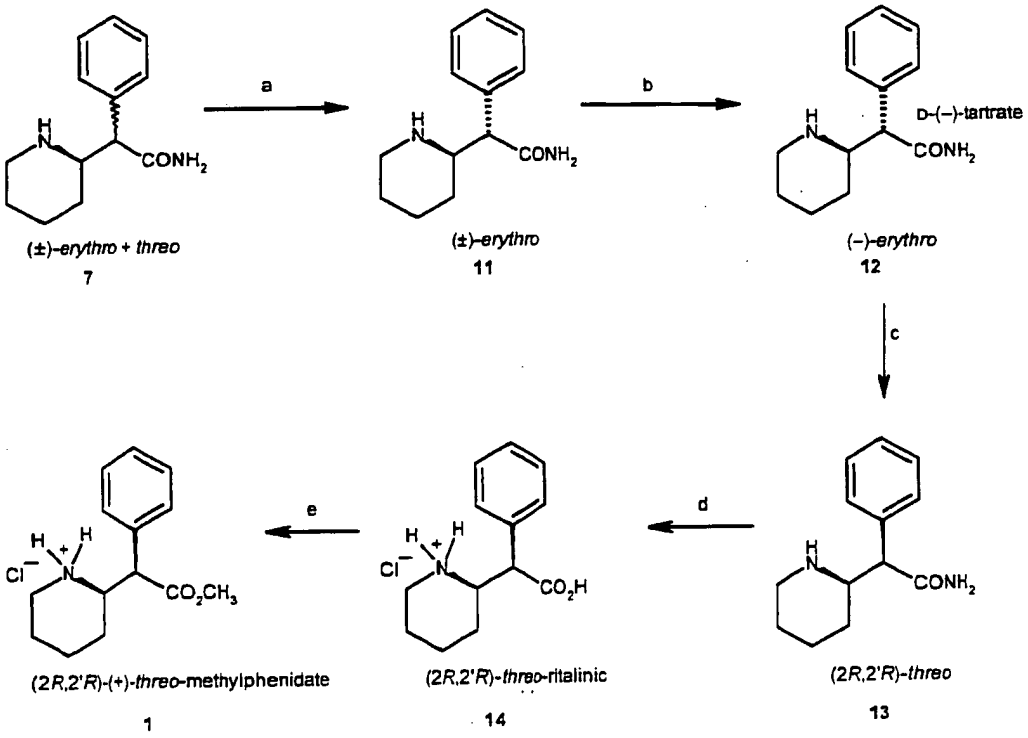
(±)-*threo*

(±)-*threo*-ritalinic acid

(±)-*threo*-methylphenidate

(a) NaOH; (b) H_2SO_4; (c) H_2, Pt, CH_3CO_2H; (d) KOH, H_2O; (e) H_2SO_4, H_2O (f) CH_3OH, HCl.

Scheme 1.



(±)-*erythro* + *threo*
7

(±)-*erythro*
11

(−)-*erythro*
12

(2*R*,2'*R*)-*threo*
13

(2*R*,2'*R*)-*threo*-ritalinic
14

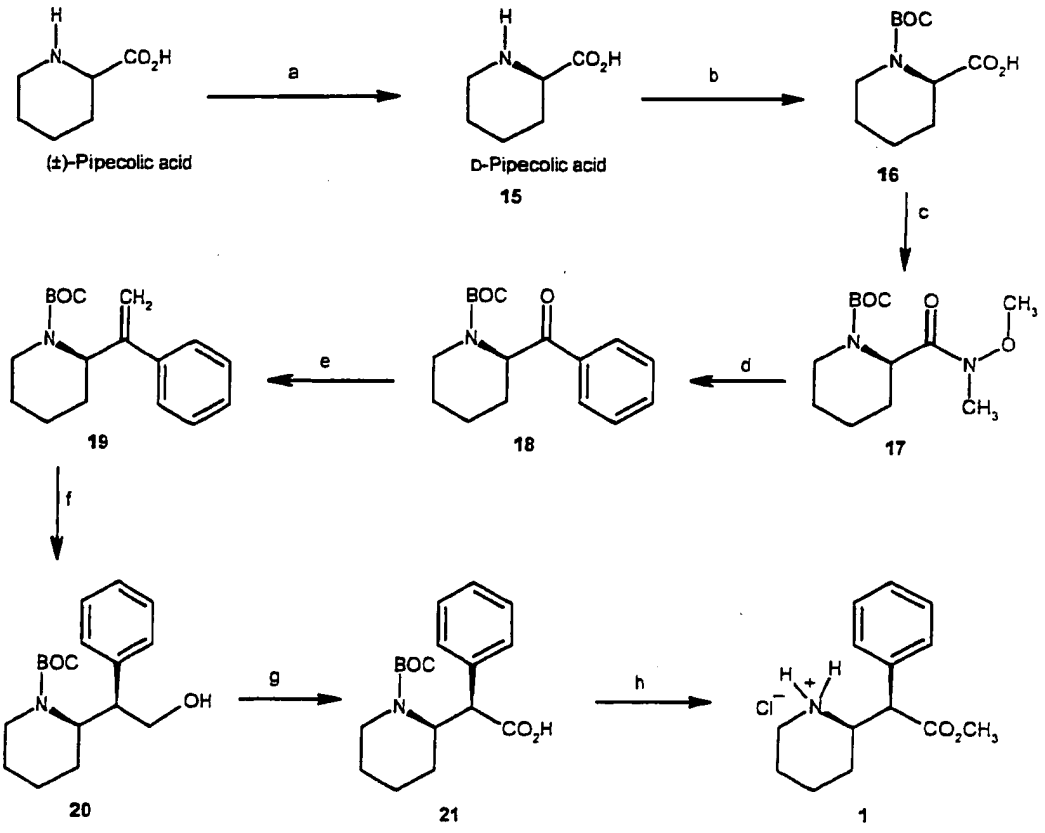
(2*R*,2'*R*)-(+)-*threo*-methylphenidate
1

(a) C_2H_5OH, HCl gas; (b) D-(−)-tartaric acid, C_2H_5OH; (c) 50% KOH, reflux, recrystallization;
(d) 6 N HCl; (e) CH_3OH, HCl.
or
(b) D-(−)-tartaric acid, CH_3OH (40%); (c) *t*-BuOK, toluene, 70 °C (85%); (d) H_2SO_4; (e) CH_3OH, HCl (80%).

Scheme 2.

ni.[22,23] Resolution of (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (11) with D-(–)-tartaric acid in methanol also afforded a 40% yield of L-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12). Epimerization of L-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12) with potassium *tert*-butoxide in toluene at 70 °C furnished (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)-acetamide (13) in 85% yield, which was converted to the desired methyl ester (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) by treatment with concentrated sulfuric acid in refluxing methanol and HCl salt preparation in 80% yield.[22,23]

Another synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) using an enantiomerically pure starting material, D-pipecolic acid (15), was reported by Perel et al. (Scheme 3).[24] Enantiomerically pure D-pipecolic acid (15) was obtained in 37% yield by recrystallization of diastereomeric tartrate salt, followed by the separation of the desired amino acid from tartaric acid by ion-exchange chromatography. D-Pipecolic acid (15) was protected with a BOC group to afford *N*-BOC-D-pipecolic acid (16) in 97% yield. The key amino ketone (18; Scheme 3) was prepared from *N*-BOC-D-pipecolic acid (16) in two steps involving its conversion to the *N*-methoxy-*N*-methyl amide 17, followed by the reaction of amide 17 with phenyllithium. The amino ketone 18 underwent a Wittig olefination with methyltriphenylphosphonium bromide in the presence of potassium *tert*-butoxide to give the alkene 19 in high yield. The transformation of alkene 19 to the desired *threo* diastereomer of alcohol 20, via hydroboration/oxidation, was critical to introduce the second stereogenic center. The *threo* isomer was favored with non- and disubstituted boranes while the *erythro* alcohol was the major isomer in the presence of monosubstituted thexylborane. Only the *threo* isomer was isolated by hydroboration of alkene 19 with (+)-IPC-BH_2 in 55% yield. Hydroboration with BH_3·THF gave a 72:28 mixture of *threo* and *erythro* isomers, respectively, from which the *threo* alcohol 20 was isolated in the highest yield (64%) after chromatography. Oxidation of *threo* alcohol 20 with PDC in DMF followed by esterification of the resulting acid 21 with diazomethane, and *N*-BOC group deprotection with 3 N methanolic HCl furn-



(a) (i) L-tartaric acid (ii) recrystallizaton (iii) ion-exchange chromat. (37%); (b) $(BOC)_2O$, $(C_2H_5)_3N$ (97%); (c) BOP, $(C_2H_5)_3N$, CH_3NHOCH_3.HCl (93%); (d) PhLi (47%); (e) CH_3PPh_3Br, *t*-BuOK (93%); (f) BH_3·THF, NaOH, H_2O_2 (64%); (g) PDC, DMF (100%); (h) (i) CH_2N_2 (ii) HCl (67%).

Scheme 3.

ished (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 67% yield after recrystallization from ethanol/ether.

4 Classical Resolution Approaches

A resolution process is more attractive and economical if the undesired enantiomer can be recycled via racemization. However, in the case of methylphenidate, such a racemization is challenging because there are two stereogenic centers which have to be epimerized. A method to affect the racemization at both stereogenic centers has been demonstrated by refluxing a solution of (2*R*,2'*R*)-*threo*-methylphenidate (1) with propionic acid in toluene to afford a mixture of four stereoisomers in roughly equal proportions.[26] Although the exact mechanism has not been ascertained, it probably involves the opening of the ring via protonation of the piperidine nitrogen. The putative olefinic intermediate has no chirality and recloses to a racemic mixture. These results suggested that the recycling of the undesired enantiomer is possible.

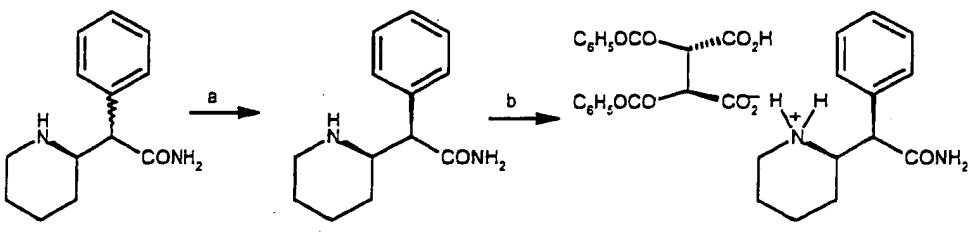
4.1 Resolution of Amide and Acid Derivatives of 1

Resolution of (±)-*threo*-ritalinic acid hydrochloride salt with (*S*)-(−)-α-methylbenzylamine in a mixture of ethanol and water (95:5 v/v) gave the diastereomeric salt enriched with (2*R*,2'*R*)-*threo*-ritalinic acid with 77% ee.[27] Ritalinic acid itself did not undergo any effective degree of resolution with any of a wide range of resolving agents. A novel double salt may have been formed from (±)-*threo*-ritalinic acid hydrochloride as a hydrate. Esterification and enrichment of the resulting enriched (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride with methanol and *tert*-butyl methyl ether would furnish 1 in high enantiomeric purity.

Resolution of (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (8; Scheme 4), obtained by epimerization of a mixture of (±)-*erythro*- and (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamides with potassium *tert*-butoxide in toluene at 70 °C, with dibenzoyl-D-tartaric acid (D-DBTA) in 2-propanol to afford (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)acetamide dibenzoyl-D-tartrate salt (22) in 40% yield has also been achieved.[25] The diastereomeric salt 22 would furnish enantiomerically pure 1 after hydrolysis and esterification.

4.2 Resolution of (±)-*threo*-Methylphenidate (10)

Since racemic (±)-*threo*-methylphenidate hydrochloride (10) is readily available, its resolution would provide a practical method for the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1). The resolution of (±)-*threo*-methylphenidate (10) was first reported by Patrick et al. in 1987 using (*R*)-(−)-binaphthyl-2,2'-diyl hydrogen phosphate (BNDHP) as the resolving agent (Scheme 5).[7] The (±)-*threo*-methylphenidate hydrochloride (10) was first converted to the free base by treatment with aqueous sodium carbonate and extracted with ether. Removal of ether furnished the (±)-*threo*-methylphenidate (10) free base. Resolution of the free base with BNDHP in a warm mixture of acetone and methanol (95:5) followed by cooling to 5 °C gave the diastereomeric BNDHP salt 23 in 45% yield which was enriched with (2*R*,2'*R*)-(+)-*threo*-methylphenidate. The enantiomeric purity of this salt 23, as determined by GC, was 85–90%. A further recrystallization of this crude salt with a mixture of acetone and methanol (98:2) increased the enantiomeric purity to 95 to 97%. Conversion of this diastereomeric BNDHP salt to the free base and HCl salt formation with ethereal HCl gave the crude (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride salt (1). A recrystallization of this HCl salt from methanol and ether furnished 1 in 99% enantiomeric purity. However, this method was found to be non-reproducible and furnished 1 with only 92.6% ee (2*R*,2'*R*:2*S*,2'*S* = 96.3:3.7).[28] Both of these reports lacked critical experimental details, in particular the volume of the sol-



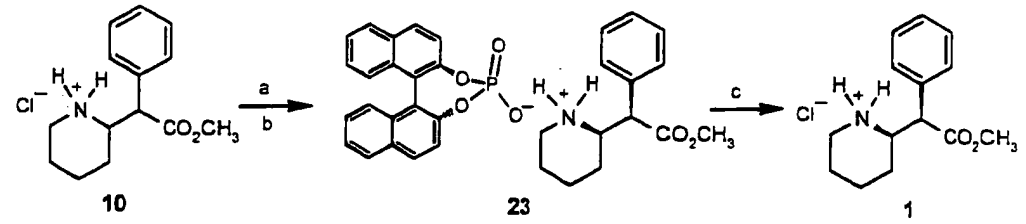
(a) *t*-BuOK, toluene, 70 °C; (b) dibenzoyl-D-(−)-tartaric acid, 2-propanol (40%).

Scheme 4.

vent used in the resolution and recrystallization steps. Subsequently, we (Novartis) reported that the resolution of (±)-*threo*-methylphenidate free base with BNDHP under the literature conditions (except unknown solvent volume) gave a diastereomeric salt with poor enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 62.8:37.2). After a detailed investigation, we (Novartis) discovered that the resolution of (±)-*threo*-methylphenidate free base in acetone–methanol mixture (98:2) with 0.5 equivalents of BNDHP, instead of 1.0 equivalent, gave the diastereomeric salt in 31% yield with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 100:0).[29,30] These results demonstrated a rare example where the use of 0.5 equivalents of the resolving agent gave excellent resolution compared to 1.0 equivalent of the same resolving agent. A practical process for the resolution of (±)-*threo*-methylphenidate free base with 0.5 equivalents of BNDHP in a mixture of isopropyl acetate and methanol (85:15 v/v) was developed by us to afford the diastereomeric BNDHP salt (23; Scheme 5) of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 36% yield with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.2:0.8).[29,30] No extra recrystallizations were necessary to enhance the enantiomeric purity of the diastereomeric BNDHP salt. This diastereomeric salt was then converted to enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) by free base generation and HCl salt formation in an overall yield of 31.4% with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.9:0.1). To avoid a step for free-base generation, a direct resolution of the (±)-*threo*-methylphenidate hydrochloride salt (10) with BNDHP in the presence of 4-methylmorpholine, which generates the free base *in situ*, in a mixture of methanol and water (1.6:1 v/v), was also reported to afford the (2*R*,2'*R*)-(+)-*threo*-methylphenidate BNDHP salt with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.1:0.9) and in 27% yield.

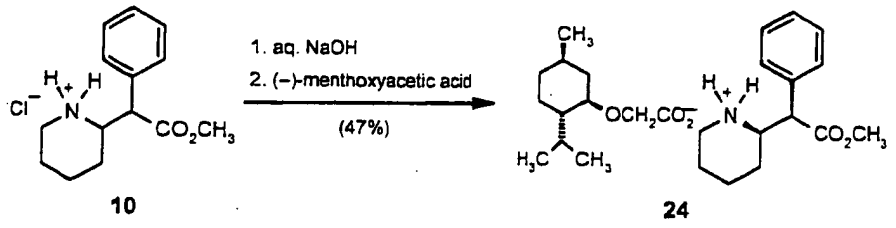
Recently, resolution of (±)-*threo*-methylphenidate (10) free base with (–)-menthoxyacetic acid in 2-propanol was reported by Zavareh (Scheme 6) to afford (–)-menthoxyacetate salt 24 of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 47% yield and 98% ee.[31]

Because both (*R*)-(–)-binaphthyl-2,2'-diyl hydrogen phosphate (BNDHP) and (–)-menthoxyacetic acid are relatively expensive, the search for a less-expensive resolving agent continued. Harris et al. reported the

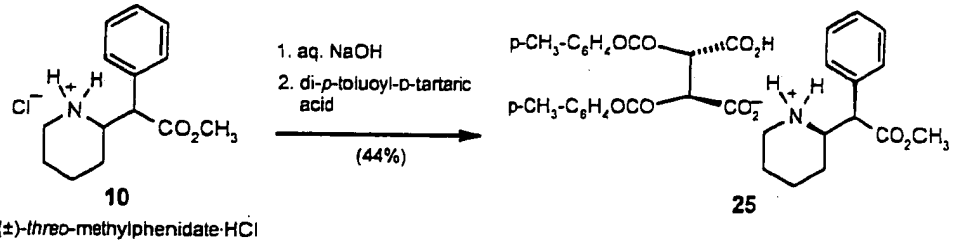


(a) aq. NaOH; (b) (*R*)-(–)-binaphthyl-2,2'-diyl hydrogen phosphate (36%); (c) (i) aq. NaOH, *i*-PrOAc (ii) conc. HCl (iii) water–conc. HCl (recrystallization).

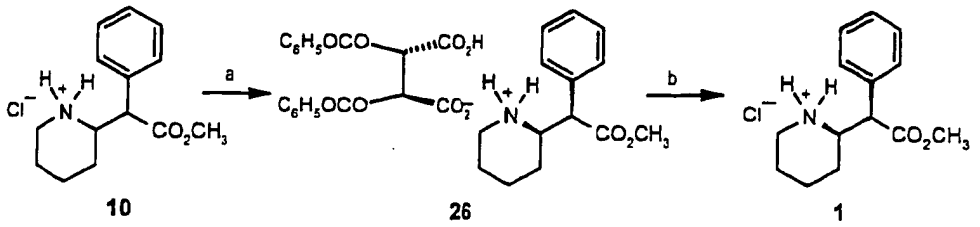
Scheme 5.



Scheme 6.



Scheme 7.



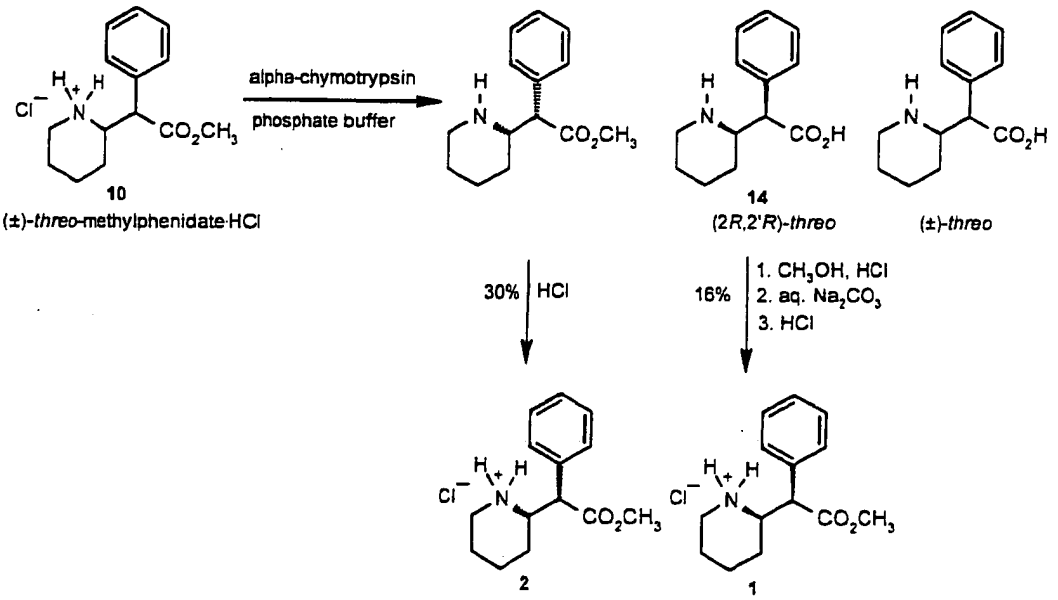
(a) dibenzoyl-D-(−)-tartaric acid, 4-methylmorpholine, CH_3OH–water (44%); (b) (i) aq. NaOH, *i*-PrOAc (ii) conc. HCl (iii) water–conc. HCl (recrystallization).

Scheme 8.

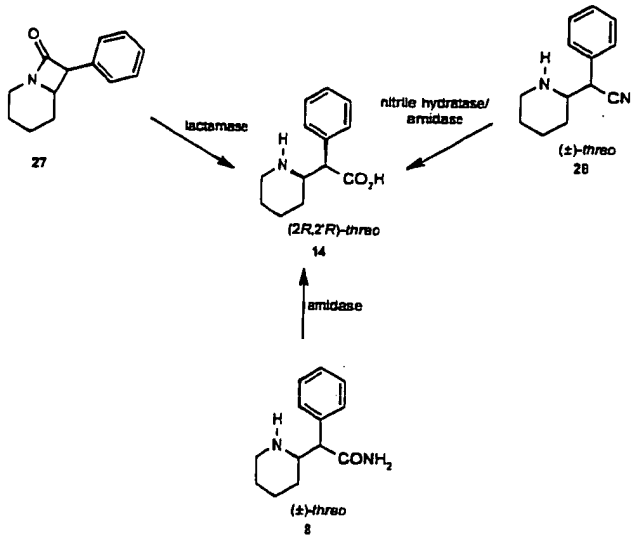
resolution of (±)-*threo*-methylphenidate (**10**) free base, generated from the HCl salt by base treatment, with the cheaper *O,O'*-di-*p*-toluoyl-D-tartaric acid in acetone containing 2% of methanol (Scheme 7).[28] It afforded the *O,O'*-di-*p*-toluoyl-D-tartrate (D-DPTTA) salt **25** of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 44.3% yield and 97% ee. The enantiomeric purity of this salt was further enhanced to >99% ee and in 92% recovery by reslurrying it in acetone containing 2% of methanol. We (Novartis) also reported an efficient and large scale resolution of the (±)-*threo*-methylphenidate hydrochloride salt with the much cheaper *O,O'*-dibenzoyl-D-tartaric acid (Scheme 8).[32,33] An advantage of these new conditions was that the (±)-*threo*-methylphenidate hydrochloride salt (**10**) was used directly for the resolution, thus avoiding the necessity for the generation of the free base. Thus, a direct resolution of (±)-*threo*-methylphenidate hydrochloride salt (**10**) with 1.0 equivalent of *O,O'*-dibenzoyl-D-tartaric acid in the presence of 1.0 equivalent of 4-methylmorpholine in a mixture of methanol and water (2:1 v/v) afforded *O,O'*-dibenzoyl-D-tartrate (D-DBTA) salt **26** of (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 38% yield with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = 99.54:0.46). The yield was further increased to 44%, without any loss of enantiomeric purity, by cooling the mixture to 0 °C. The *O,O'*-dibenzoyl-D-tartrate salt of (2*R*,2'*R*)-(+)-*threo*-methylphenidate was then converted to (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (**1**) in 40% overall yield (from **10**) with excellent enantiomeric purity (2*R*,2'*R*:2*S*,2'*S* = >99.9:<0.1).

5 Enzyme-Based Resolution Approaches

The resolution of (±)-*threo*-methylphenidate (**10**) free base by enantioselective enzymatic hydrolysis was first reported by us (Novartis) (Scheme 9).[20] α-Chymotrypsin and subtilisin carlsberg exhibited selectivity towards the hydrolysis of the (2*R*,2'*R*)-enantiomer.

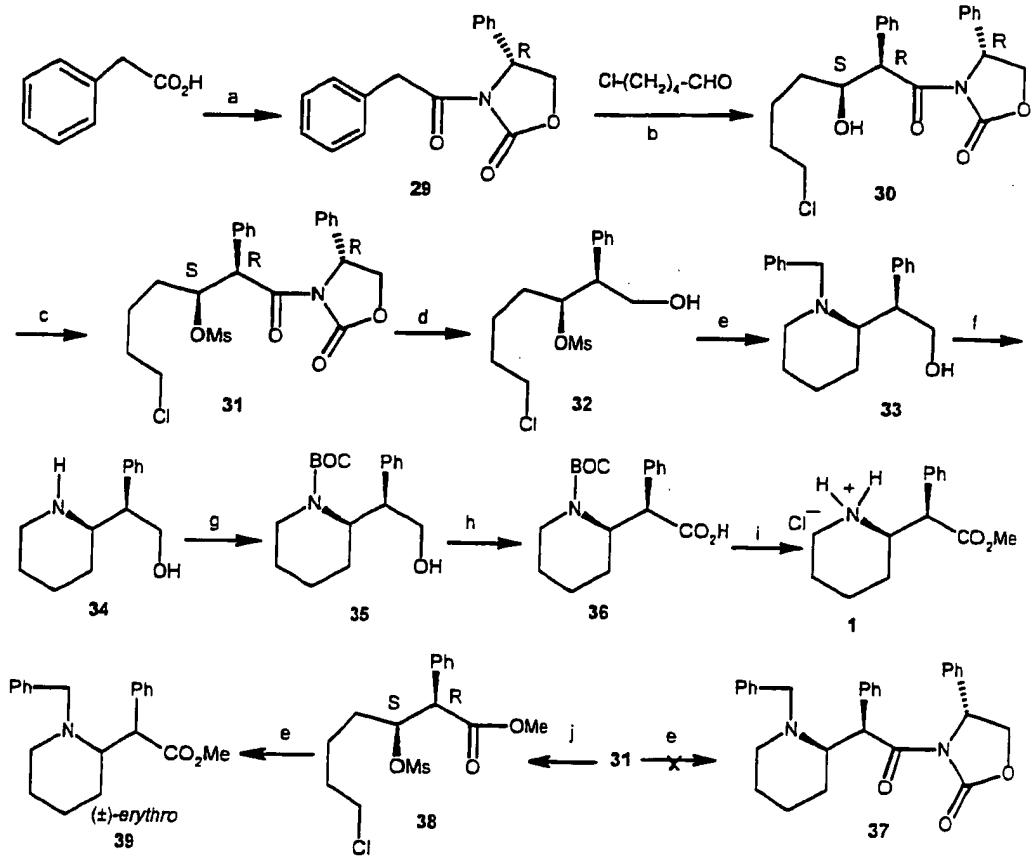


Scheme 9.



Scheme 10.

Hydrolysis of (±)-*threo*-methylphenidate (10) free base with α-chymotrypsin in pH 7.0 phosphate buffer furnished a heterogeneous mixture from which enantiomerically pure (2*S*,2'*S*)-(–)-*threo*-methylphenidate hydrochloride (2) was isolated in 30% yield with >99% ee after extractive work-up and conversion of the free base to the HCl salt. The solid, which precipitated during the enzymatic hydrolysis in 30% yield, was identified as racemic (±)-*threo*-ritalinic acid. It was formed as a result of the hydrolysis of some of the (2*S*,2'*S*)-enantiomer. The (2*R*,2'*R*)-*threo*-ritalinic acid (14) was highly soluble in the aqueous medium and did not precipitate. It was isolated from the aqueous layer by lyophilization, esterification with methanol, and basic work-up to afford (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base in 80% ee. Treatment of this free base with HCl gas followed by recrystallization of the resulting HCl salt from a mixture of methanol and *t*-butyl methyl ether (1:1.7 v/v) afforded (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydro-



(a) (*R*)-4-phenyl-2-oxazolidinone, pivaloyl chloride, Et_3N, toluene (78%); (b) i) *n*-Bu_2BOTf, DIEA, CH_2Cl_2 or toluene, –20 °C to RT, ii) 30% H_2O_2, MeOH (78%); (c) Ms_2O, C_5H_5N, 0 °C or MsCl, Et_3N (92%); (d) $NaBH_4$, THF–H_2O, 0 °C to RT (91%); (e) $PhCH_2NH_2$ (10 eq.), 85 °C, 3 h (60%); (f) H_2, 10% Pd-C, EtOH (92%); (g) $(BOC)_2O$, THF (82%); (h) $NaIO_4$, $RuCl_3{\cdot}H_2O$, CH_3CN, H_2O, CCl_4 (80%); (i) MeOH, HCl, 50 °C, overnight (70%); (j) MeOLi, MeOH, 0 °C (50%).

Scheme 11.

chloride (1) in 16% yield and >98% ee. Thus, the differences in the solubilities of the (±)- and (2*R*,2'*R*)-*threo*-ritalinic acids in the aqueous medium led to selective crystallization of the former during enzymatic hydrolysis and made their separation possible. Similar results were obtained using subtilisin carlsberg as the enzyme yielding (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 15% yield with >98% ee, and (2*S*,2'*S*)-(−)-*threo*-methylphenidate hydrochloride (2) in 26% yield with >99% ee.

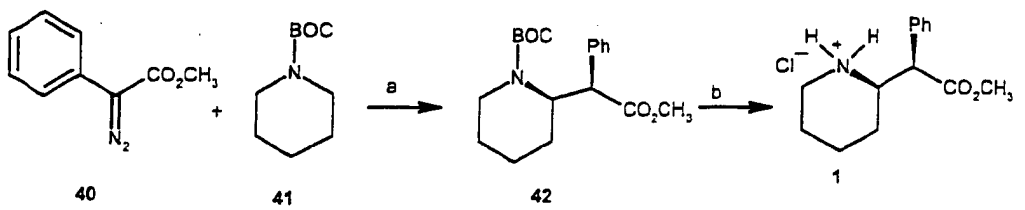
Enzymatic hydrolysis of (±)-*threo*-methylphenidate (10) free base with an esterase/lipase enzyme, obtained from various microorganisms, was also reported by Zeitlin et al.[34] to furnish (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 96% ee. (±)-*trans*-7-Phenyl-1-azabicyclo[4.2.0]octan-8-one (27) was also hydrolyzed using a lactamase enzyme in pH 7 phosphate buffer (Scheme 10) to afford (2*R*,2'*R*)-*threo*-ritalinic acid (14) with >96% ee. (2*R*,2'*R*)-*threo*-Ritalinic acid (14) was also obtained by hydrolysis of (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (8) with amidase or (±)-*threo*-2-phenyl-2-(2-piperidyl)acetonitrile (28) using a nitrile hydratase and amidase enzymes in 98% ee.[34] (2*R*,2'*R*)-*threo*-Ritalinic acid would furnish (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride 1 after esterification and HCl salt formation.

6 Enantioselective Synthesis Approaches

We (Novartis) reported the first enantioselective synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1), which involved an asymmetric aldol condensation of 5-chlorovaleraldehyde with the (*Z*)-boron enolate derived from *N*-phenylacetyl-(*R*)-4-phenyl-2-oxazolidinone (29) as the key step to generate both stereogenic centers of 1 with desired absolute configuration (Scheme 11).[35]

Reaction of 5-chlorovaleraldehyde with the (*Z*)-boron enolate derived from *N*-phenylacetyl-(*R*)-4-phenyl-2-oxazolidinone (29) afforded the desired single diastereomer 30, as confirmed by ^{1}H NMR, in 78% yield. Mesylation of 30 with either methanesulfonic anhydride and pyridine in dichloromethane or methanesulfonyl chloride and triethylamine in toluene yielded the mesylate 31 in 92% yield. Attempts to construct the piperidine ring by the cyclization of 31 to 37 by treatment with benzylamine at 85 °C gave a complicated mixture. It was postulated that the undesired ring opening of the 2-oxazolidinone by benzylamine and the steric bulk of this chiral auxiliary may be responsible for this unexpected outcome. Alternatively, the methyl ester 38 underwent cyclization with benzylamine, however, the product was characterized to be (±)-*erythro*-methylphenidate 39. These results could be explained based on the elimination of the mesylate, which destroyed both stereogenic centers to furnish the α,β-unsaturated ester intermediate, which then underwent a Michael addition with benzylamine, followed by cyclization. To circumvent this problem, the methyl ester group was replaced with the corresponding alcohol function prior to the cyclization, which could be oxidized back to the desired carboxylic ester functionality afterwards. Reductive removal of the chiral auxiliary in 31 with sodium borohydride in THF and water yielded the desired alcohol 32 in 91% yield. Treatment of alcohol 32 with benzylamine at 85 °C afforded the desired piperidine intermediate 33 in 60% yield. Hydrogenation of 33 with 10% Pd-C in ethanol furnished the amino alcohol 34 in 92% yield, which was acylated with di-*tert*-butyl dicarbonate to afford the *N*-BOC-protected alcohol 35 in 82% yield. Oxidation of alcohol 35 with $NaIO_4$ and $RuCl_5$ furnished the acid 36 in 80% yield. Treatment of acid 36 with methanol in the presence of HCl gas at 50 °C gave the desired (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 70% yield. The enantiomeric purity of 1 was >99% ee and the overall yield from phenylacetic acid was 13% after 9 steps.

Winkler et al. reported[36–37] an enantioselective synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) based on the rhodium-mediated C–H insertion of methyl phenyldiazoacetate (40) with *N*-BOC-piperidine (41). Thus, reaction of methyl phenyldiazoacetate (40) with *N*-BOC-piperidine (41;



40 41 42 1

(a) Rh_2(5*R*-MEPY)$_4$, cyclohexane, 50 °C; (b) HCl, CH_3OH
or
(a) Rh_2(*S*-biDOSP)$_2$, 2,3-dimethoxybutane, RT; (b) TFA

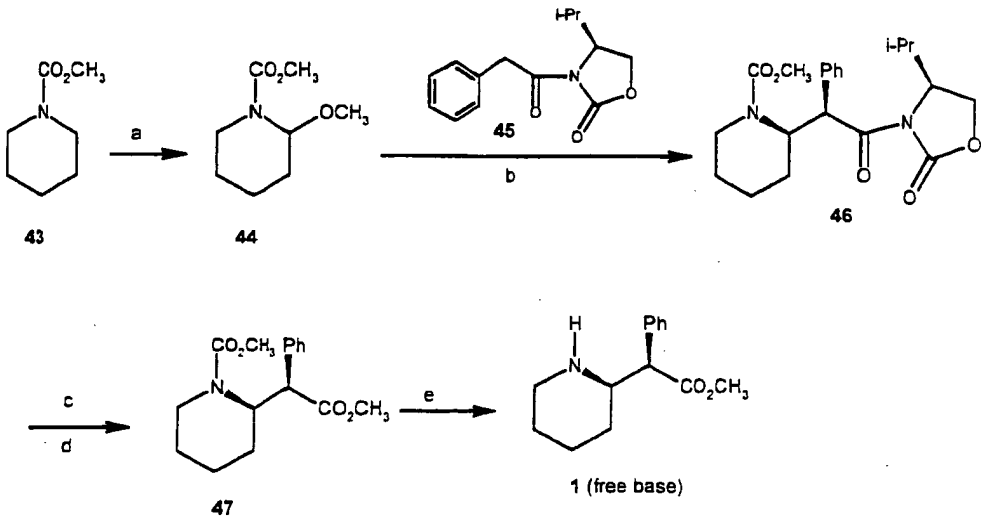
Scheme 12.

Scheme 12) in cyclohexane at 50 °C in the presence of 1 mol % of $Rh_2(5R\text{-MEPY})_4$ led to the selective formation of *N*-BOC-D-*threo*-methylphenidate (42) in 64.5% yield. Deprotection of 42 with HCl gas in methanol furnished crude (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride (1) in 68.5% yield with 94% de and 69% ee. Two recrystallizations of this crude product from a mixture of ethanol and diethyl ether (1:1 v/v) gave 1 in 26% yield with 95% de and >95% ee.

Independently, Davies et al.[38] also reported the same approach as described above by Winkler et al. The $Rh_2(S\text{-DOSP})_4$-catalyzed decomposition of methyl phenyldiazoacetate (40) in the presence of *N*-BOC-piperidine (41, 4 equivalents) in 2,3-dimethylbutane at room temperature, followed by treatment with trifluoroacetic acid, resulted in the formation of a mixture of *threo*- and *erythro*-methylphenidate in 49% yield. However, the *threo*-isomer was the minor diastereomer and was formed in only 34% ee. A major improvement in enantioselectivity and diastereoselectivity was achieved by carrying out the reaction with the $Rh_2(S\text{-biDOSP})_2$ catalyst. The ratio of *threo* to *erythro* isomers was improved to 2.5:1 (73% yield), respectively. The (2*R*,2'*R*)-*threo*-isomer was formed in 86% ee and isolated in 52% yield.

Matsumura et.al.[39,40] described a convenient method for the preparation of (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base starting from the easily available *N*-methoxycarbonylpiperidine (43; Scheme 13) involving a highly stereoselective coupling reaction of the α-methoxylated carbamate 44 with the Evans imide 45 as the key step. An electrochemical α-methoxylation of 43 in methanol afforded the *N*-protected α-methoxypiperidine 44 in 85% yield. The C–C bond forming reaction between 44 and 45 was successfully achieved by using a combination of $TiCl_4$ and diisopropylethylamine (DIPEA) to give the coupled product 46 with high diastereo- and enantioselectivity. The configuration of 46 was determined at the stage of 47 and 1 by chiral stationary phase HPLC analysis. The ratio of *erythro*-47 to *threo*-47 was 5.3:94.7 and the ee of the *threo* isomer was 99.6%. The predominant formation of the (2*R*,2'*R*)-isomer formation suggested that the reaction might proceed through a coordinated intermediate in which the acyliminium ion generated from 44 approaches the thermodynamically stable *Z*-form of the titanium enolate generated from 45 from the *si* face. Treatment of the carbamate 46 with LiOH in the presence of H_2O_2, followed by the treatment of the resulting acid with CH_2N_2, furnished the methyl ester 47 in 54% yield. The deprotection at the *N*-methoxycarbonyl group with $(CH_3)_3SiI$ afforded (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base in 75% yield.

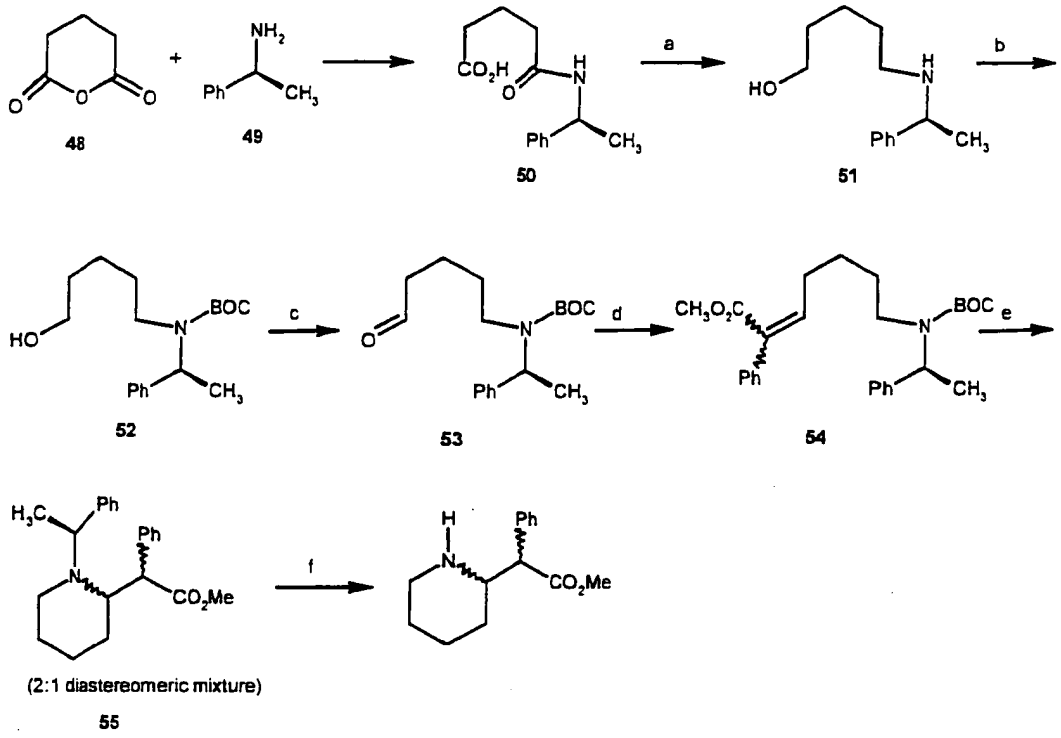
Fox et al.[41,42] reported an approach involving an intramolecular Michael addition as the key step (Scheme 14) and utilizing (*S*)-α-methylbenzylamine as the chiral auxiliary, towards a potential synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) free base. Ring opening of glutaric anhydride (48) with (*S*)-α-methylbenzylamine (49) furnished the acid 50. Reduction of 50 afforded the amino alcohol 51 in 78% yield. Protection of the secondary amine with $(BOC)_2O$ followed by Swern oxidation gave the alde-



(a) 2.3 F/mol of electricity in CH_3OH containing $(C_2H_5)_4NBF_4$, (85%) (b) $TiCl_4$, DIPEA, CH_2Cl_2, –78 °C to RT; (c) LiOOH, THF–water, RT; (d) CH_2N_2, ether, RT (54% from **45**); (e) $(CH_3)_3SiI$, CH_2Cl_2, RT (75%).

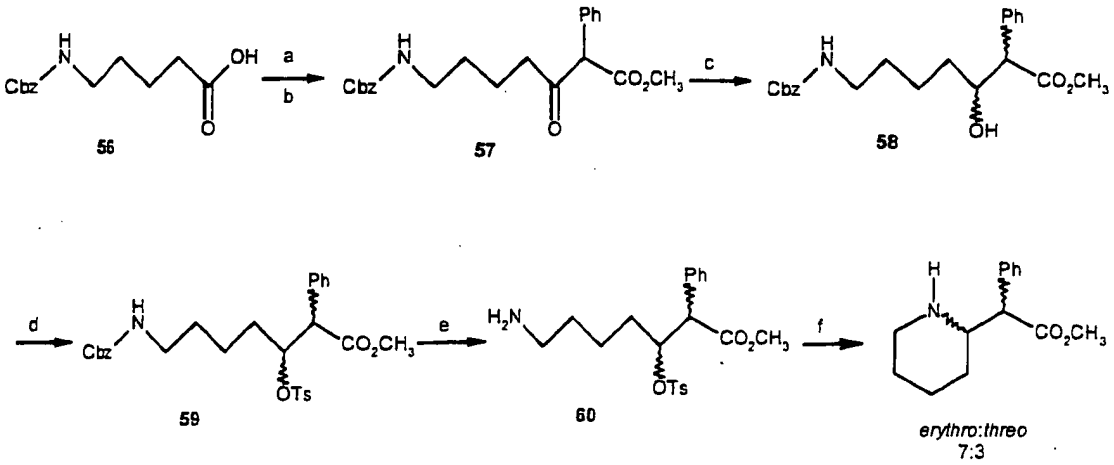
Scheme 13.

hyde 53 in 68% yield. Horner-Wadsworth-Emmons olefination of 53 afforded the α,β-unsaturated ester 54 as a mixture of geometrical isomers. Treatment of 54 in the presence of lithium diethylamide in THF led to the cyclization of only one regioisomer to give a 2:1 mixture of diastereomers 55. As four diastereomers



(a) reduction (78%); (b) $(BOC)_2O$, THF–2 M NaOH (89%); (c) DMSO, oxalyl chloride, $(C_2H_5)_3N$ (68%); (d)(i) methyl 2-bromophenylacetate, triethylphosphite (ii) NaHMDS, THF (66%); (e) (i) TFA (ii) $(C_2H_5)_3N$ (iii) lithium diethylamide, THF, –78 °C; (f) hydrogenation.

Scheme 14.



(a) *N,N'*-carbonyldimidazole, THF; (b) $PhCH_2CO_2CH_3$, LDA (66.4%); (c) [RuI(*p*-cymene)(S)-binap]I, cat. tin chloride, camphor-10-sulfonic acid, H_2, CH_3OH, 80 °C (87.4%); (d) *p*-toluenesulfonyl chloride, pyridine, cat. DMAP (61.8%); (e) H_2, 5% Pd-C; (f) K_2CO_3, CH_3OH (77.5%).

Scheme 15.

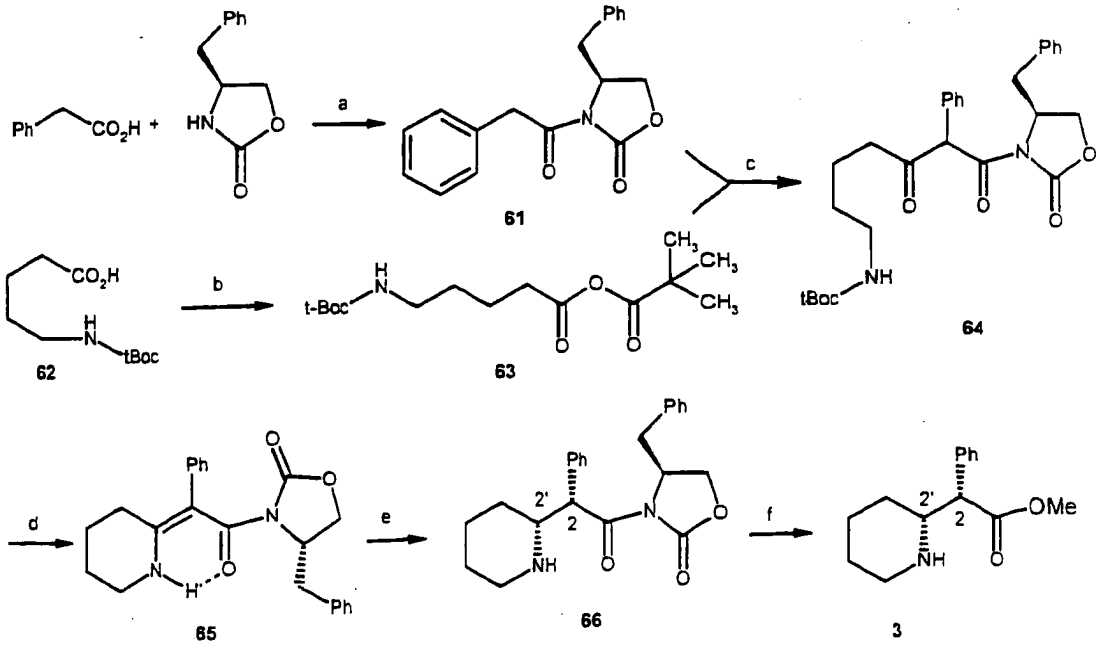
could be produced in this cyclization, this represents good distereoselectivity. The diastereomeric mixture 55 was hydrogenated to afford a diastereomeric mixture of 1. Neither the enantiomeric purity nor the characterization of the diastereomers was reported.

Another potential approach towards 1 was reported by Seido et al.[45] utilizing an asymmetric reduction of the ketone (57; Scheme 15) as the key step. Acylation of the lithium enolate of methyl phenylacetate with the imidazolide, obtained by treatment of the acid 56 with *N,N'*-carbonyldiimidazole, gave the ketoester 57 in 66.4% yield. Asymmetric reduction of 57 with [RuI(*p*-cymene)(*S*)-binap]I, tin chloride, and camphor-10-sulfonic acid in methanol at 80 °C afforded the alcohol 58 as a mixture of *syn* and *anti* forms in 87.4% yield. The ratio of *syn* to *anti* isomers was 76.3:23.7 and the enantiomeric purity of each form was 95.6% ee and 97.8% ee, respectively. Tosylation of 58 with *p*-toluenesulfonyl chloride and pyridine in the presence of catalytic amounts of DMAP yielded a diastereomeric mixture of tosylate 59 in 61.8% yield. Deprotection of the *N*-Cbz group in 59 by hydrogenation over 5% Pd-C followed by cyclization of the resulting amino tosylate 60 with potassium carbonate in methanol furnished methylphenidate as a mixture of *erythro* and *threo* isomers in a 7:3 ratio and 77.5% yield.

7 Approaches Based on Enantioselective Synthesis of (2*S*,2'*R*)-*erythro*-Methylphenidate and Epimerization

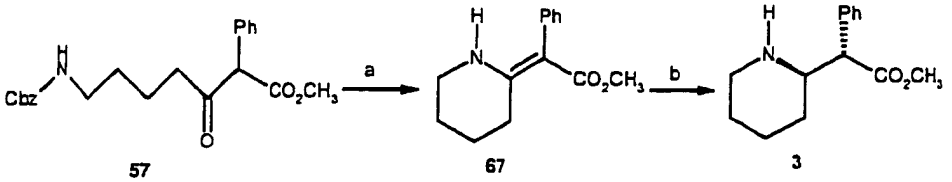
Because epimerization of (2*S*,2'*R*)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide (12; Scheme 2) at the benzylic stereogenic center is known to afford (2*R*,2'*R*)-*threo*-2-phenyl-2-(2-piperidyl)acetamide (13), enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate (3) would provide a feasible approach to (2*R*,2'*R*)-(+)-*threo*-methylphenidate (1) after epimerization.

We (Novartis) reported[44] an enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate (3) utilizing Evans (*S*)-4-benzyl-2-oxazolidinone chiral auxiliary to control the diastereofacial selectivity in the hydrogenation of enamine intermediate (65; Scheme 16). Acylation of (*S*)-4-benzyl-*N*-phenylacetyl-2-oxazolidinone (61) with the mixed anhydride 63, followed by deprotection of the *N*-Boc group with TFA, and neutralization of the reaction mixture with $NaHCO_3$ afforded the enamine intermediate 65. Hydrogenation of enamine 65 with 10% Pd-C in ethyl acetate furnished 66 in 95% yield with an excellent diastereoselectivity (97:3). Treatment of 66 with methanol in the presence of LnI_3 afforded the desired



(a) *t*-BuCOCl, Et_3N, $PhCH_3$, 80 °C, 12 h (85%); (b) *t*-BuCOCl, Et_3N, $PhCH_3$, RT, 4 h (100%); (c) LiHMDS, THF, −78 °C to RT, 4 h; (d) i) TFA, CH_2Cl_2, 0 °C to RT, 4 h, ii) $NaHCO_3$ (30% in two steps); (e) 10% Pd-C, EtOAc, RT, 24 h (95%); (f) MeOH, LnI_3, THF, RT, 16 h (85%).

Scheme 16.



(a) H_2, 5% Pd/C, CH_3OH (93.9%); (b) H_2, [RuI(p-cymene)((*R*)-H8-binap)], CH_3OH, HCl, 50 °C (98.7%).

Scheme 17.

(2*S*,2'*R*)-*erythro*-methylphenidate (3) in 85% yield. The enantiomeric purity of 3 was excellent (2*S*,2'*R*:2*R*,2'*S* = 97:3).

Another synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate (3) was reported by Seido et al.[45] involving asymmetric hydrogenation of enamine 67 as the key step (Scheme 17). Deprotection of the *N*-Cbz group in ketoester 57 by hydrogenation over 5% Pd-C gave the enamine 67 in 95% yield. Asymmetric hydrogenation of 67 with [RuI(*p*-cymene)((*R*)-H8-binap)] in methanol containing HCl at 50 °C furnished (2*S*,2'*R*)-*erythro*-methylphenidate (3) in 98.7% yield and the ratio of *erythro* to *threo* diastereomers was 99:1. The enantiomeric purity of the *erythro* isomer was 99.4% ee. Hydrogenation using (*R*)-Tol-BINAP as the ligand afforded a mixture of *erythro* and *threo* isomers in a 99.1:0.9 ratio, respectively, which was epimerized to a 26.6:73.4 mixture of *erythro* to *threo* isomers, respectively, with 88.8% ee of the *threo* isomer.

8 Conclusions

After the first preparation of enantiomerically pure (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride (1) in 1958, it is only recently that a great deal of interest has been demonstrated in the synthesis of this molecule. Various approaches to the preparation of enantiomerically pure (2*R*,2*R*)-(+)-*threo*-methylphenidate hydrochloride (1) are reviewed. These approaches include synthesis using enantiomerically pure precursors obtained by resolution, classical and enzyme-based resolution approaches, enantioselective synthesis approaches, and approaches based on enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate followed by epimerization at the 2-position. Classical resolution approaches have been successfully upscaled to produce 1 on a multi-kilogram scale due to the ready availability of racemic (±)-*threo*-methylphenidate hydrochloride (**10**). While some enantioselective approaches are short, they do not provide 1 of the desired enantiomeric purity necessary for drug development. Enantioselective synthesis approaches to produce 1, however, will become viable, particularly those based on approaches reported by us (Novartis),[35] Matsumura,[39,40] and Seido.[45]

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